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Allogeneic Stem Cell Transplantation for Relapsed or Refractory Lymphoma after Conditioning with BEAM/Fludarabine/TBI

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A B S T R A C T

Allogeneic stem cell transplant (SCT) after high-dose conditioning with BEAM/fludarabine/total body irradiation (TBI) in patients with relapsed or refractory lymphoma has shown promising results in a pilot study. In this trial, we treated 50 consecutive patients with refractory or relapsed lymphoma or chronic lymphocytic leukemia (CLL). The patients included were considered to have poor-prognosis disease (eg, one-third was chemo-refractory at transplantation and more than one-half had failed previous autologous or allogeneic SCT). All patients engrafted and achieved full donor chimerism. Grade II-IV acute graft-versus-host disease (aGVHD) occurred in 64% of patients (95% confidence interval [CI], 52% to 79%), and chronic GVHD (cGVHD) in 51% (95% CI, 36% to 66%). At 3 years, overall survival was 61% (95% CI, 46% to 75%). Progression-free survival was 55% (95% CI, 40% to 70%), with 30% (95% CI, 19% to 47%) transplantation-related mortality and a relapse incidence of 15% (95% CI, 7% to 32%). Disease classification and stage as well as remission status at transplantation and type of previous treatment (including previous SCT) had no significant impact on transplantation outcome. In conclusion, allogeneic SCT after BEAM/fludarabine/TBI provides excellent tumor control with complete and durable remissions in patients with poor-prognosis lymphoma and CLL. High rates of GVHD and GVHD-related mortality associated with this regimen are a major concern and warrant modification of the regimen in the future.

INTRODUCTION

High-dose chemotherapy followed by autologous stem cell transplant (SCT) is the standard of care for lymphoma that has relapsed or is refractory to standard treatment [1]. Although curative in some cases, many patients still relapse after auto-SCT. In this situation, allogeneic SCT can provide a further rescue option [2]. Compared to autologous transplantation, allogeneic SCT holds the advantage of avoiding tumor cell contamination of the graft, provides a graft-versus-lymphoma effect, and offers the possibility of transplantation in case of autologous stem cell mobilization failure plus the possibility of donor lymphocyte infusion in event of insufficient tumor control [3,4].

The curative potential of allogeneic SCT has been demonstrated for the complete spectrum of lymphoid neoplasms including chronic lymphocytic leukemia (CLL), follicular non-Hodgkin lymphoma (NHL), aggressive NHL, Hodgkin's lymphoma (HL), and T-cell lymphoma [5-10]. Many controversies exist as to which patients should be offered allogeneic SCT, as well as to their proper assignment to the different myeloablative and reduced-intensity conditioning (RIC) regimens at hand [11]. Myeloablative conditioning regimens generally provide, at the cost of higher treatment-related mortality (TRM), improved disease control with relapse rates of less than 20%. In contrast, RIC allogeneic SCT offers lower regimen-related toxicity, at the expense of increased relapse rates [12].

We have previously reported on our experience of allogeneic SCT after conditioning with BEAM/fludarabine/total body irradiation (TBI) in 11 patients with lymphoma, an approach designed to combine the cytoreductive properties of the BEAM regimen with the graft-versus-tumor effect of allogeneic transplantation [13]. In this study, we present the final evaluation of 50 consecutive patients with poor prognosis lymphoma or CLL treated with this regimen.

MATERIALS AND METHODS

Treatment Plan

The conditioning regimen consisted of etoposide dose-intensified BEAM chemotherapy (BCNU 300 mg/m^2 i.v. once daily on day −5, etoposide 200 mg/m^2 i.v. twice daily on days −5 to −2, cytarabine 200 mg/m^2 i.v. twice daily on days −5 to −2, and melphalan 140 mg/m^2 i.v. once daily on day −1) with overlapping fludarabine 30 mg/m^2 given once daily on days −4 to −2. This was followed by a single dose of TBI (2 Gy) on the day of stem cell infusion. All patients gave written informed consent to their treatment and to having their data analyzed.

GVHD Prophylaxis and Supportive Care

Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine and a short course of mycophenolate mofetil (MMF) until day 28 (continued in the case of active GVHD) [13]. Trough cyclosporine target level was 200 ng/mL and was quantified at least once a week. MMF levels were not measured. In the absence of GVHD, cyclosporine was tapered by day 180.

All patients were treated in reverse protective isolation and received prophylaxis with valacyclovir 500 mg twice daily, fluconazole 400 mg once weekly, and co-trimoxazole 3 times a week. In the event of fever, broad-spectrum antibiotics and, when necessary, antifungal medication or ganciclovir were prescribed. Irradiated and leucodepleted blood products were administered in order to maintain a hemoglobin level above 80 g/L and platelet counts above 10 G/L. Local cryotherapy to reduce mucositis or growth factor support were not given. No peritransplantation rituximab was

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Table 1
Patient and Transplant Characteristics

Variables	N (Range)
No. of patients	50
Age, median (range)	49 (22-64)
Male/female	28/22
Comorbidities	
Sorror score 0	24
Sorror score 1-2	17
Sorror score ≥3	9
Donor	
HLA-identical sibling	29
HLA-matched unrelated	19
HLA-1 antigen mismatched unrelated	2
Disease characteristics according to histology	
• Follicular NHL (no.)	8
Initial risk score intermediate to high (FLIPI)	7
Median no. of prior chemotherapy lines (range)	6 (4-7)
Prior SCT	6
Chemorefractory disease at transplantation	3
• CLL (no.)	13
Cytogenetics del17p	5
Cytogenetics del11q	3
Median no. of prior chemotherapy lines	2 (1-5)
Chemorefractory disease at transplantation	5
• Diffuse large B cell lymphoma (no.)	8
Initial risk score intermediate to high (IPI)	7
Median no. of prior chemotherapy lines	5 (1-8)
Prior SCT	7
Chemorefractory disease at transplantation	2
• Mantle cell lymphoma (no.)	5
Initial risk score intermediate to high (MIPI)	4
Median no. of prior chemotherapy lines	2 (1-3)
Prior SCT	1
Chemorefractory disease at transplantation	1
• HL (no.)	8
Median no. of prior chemotherapy lines	6.5 (5-8)
Prior SCT	7
Chemorefractory disease at transplantation	3
• Peripheral T-cell lymphoma	6
Median no. of prior chemotherapy lines	3.5 (2-6)
Prior SCT	3
Chemorefractory disease at transplantation	1
• Others	2
Median no. of prior chemotherapy lines	4.5
Prior SCT	0
Chemorefractory disease at transplantation	1

NHL indicates non-Hodgkin lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; SCT, stem cell transplant; CLL, chronic lymphocytic leukemia; IPI, International Prognostic Index; MIPI, MCL International Prognostic Index; HL, Hodgkin's lymphoma.

planned; however, rituximab application in the context of re-induction treatment within 3 months before allo-SCT was recorded in 15 patients.

Endpoints

The primary endpoint was progression-free survival (PFS). Secondary endpoints consisted of overall survival (OS), transplant-related mortality, relapse incidence, engraftment, and regimen-related toxicity. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Severity of acute GVHD (aGVHD) and chronic GVHD (cGVHD) was rated as defined by the revised Glucksberg criteria and the National Institutes of Health consensus [14,15]. Response was assessed according to current and standardized criteria [16-19]. As previously described in the setting of myeloid neoplasms, we calculated the comorbidity risk index according to Sorror et al. [20]. Risk stratification at diagnosis of diffuse large B cell lymphoma (International Prognostic Index), follicular NHL (Follicular Lymphoma International Prognostic Index), and mantle cell lymphoma (MCL International Prognostic Index) was derived from the respective scoring systems [21-23]. "Histologically aggressive" disease included diffuse large B cell lymphoma, blastoid variant mantle cell lymphoma, peripheral T cell lymphoma, or grade 3 follicular lymphoma, whereas the remaining cases of NHL were classified as "histologically nonaggressive."

Statistical Analysis

OS and PFS were estimated by Kaplan-Meier analysis. Cumulative incidence rates of relapse and TRM were calculated by treating these events as competing outcomes. Variables affecting OS were analyzed in a multivariable fashion using Cox models, with aGVHD and cGVHD incorporated as time-dependent covariates.

RESULTS

Between 2002 and 2011, 28 male and 22 female patients ages 22 to 64 (median, 49 years) received protocol treatment for poor prognosis lymphoma. Patients had refractory or relapsed CLL (n = 13), HL (n = 8), or NHL (n = 29). The median time from initial diagnosis to transplantation was 46 months (range, 5-180 months). Patients had undergone a median of 5 previous treatment lines (range, 1-8), including autologous SCT after BEAM conditioning in 44%. Eight of the patients experienced early relapse after autologous SCT (<6 months postautograft). Five patients had undergone previous allogeneic SCT after RIC. Disease status at transplantation was progressive in 16%, stable disease in 16%, partial remission (PR) in 42%, and complete remission (CR) in 26%. This collective of 50 patients includes 9 patients who were part of our preliminary report in 2007 [13]. Further patient and disease characteristics are shown in Table 1.

Stem cell donors were either HLA-identical siblings (58%), 10/10 HLA-matched unrelated donor (38%) or 9/10 matched unrelated (4%). Stem cell source was bone marrow in 2 matched unrelated donor transplantations, and granulocyte colony-stimulating factor–mobilized peripheral blood in all remaining cases. The median CD34+ cell count infused amounted to 6.5×10^6 cells/kg.

Engraftment, GVHD, and Regimen-Related Toxicity

All evaluable patients engrafted after a median of 12 days (range, 9-27 days) and achieved full donor chimerism on day +30. The median hospitalization length was 34 days (range, 23-231 days). No patient received posttransplantation donor lymphocyte infusions. AGVHD occurred in 38 of the 50 patients (76%): grade I in 6 (12%), grade II in 10 (20%), grade III in 11 (22%), and grade IV in 11 (22%). Interestingly, 2 patients developed aGVHD after MMF discontinuation. Of the 41 patients surviving past day 100, 21 (51%) developed cGVHD (10 limited/11 extensive). GVHD was the primary cause of death in 10 patients.

Major TRM resulted from mucositis and infection in neutropenia. Neutropenic fever occurred in all patients and was treated with broad-spectrum antibiotics. Blood cultures were positive for coagulase-negative staphylococcus in 3 patients, enterococcus faecium in 2 patients, and pseudomonas aeruginosa in 1 patient. Extended-spectrum beta-lactamase *Escherichia coli* and *Candida glabrata* septicemia both occurred once. Invasive fungal infection of the lungs was diagnosed in 14 patients (9 possible, 3 probable, and 2 proven cases). Viral infections were documented in 5 patients (cytomegalovirus), 2 patients (respiratory syncytial virus), and 1 patient (norovirus) in the first month post-transplantation, respectively. Infection was the primary cause of death in 4 patients.

Mucositis was observed in all patients: severity was grade 4 in 62%, grade 3 in 30%, and grade 2 in 8% of patients. The correlation with pretransplantation renal function did not reach statistical significance. Severe bleeding complications (≥grade 3) were diagnosed in 3 patients. Two cases of diffuse alveolar hemorrhage resolved under high-dose steroid treatment, whereas cerebral hemorrhage led to the death of 1 patient.

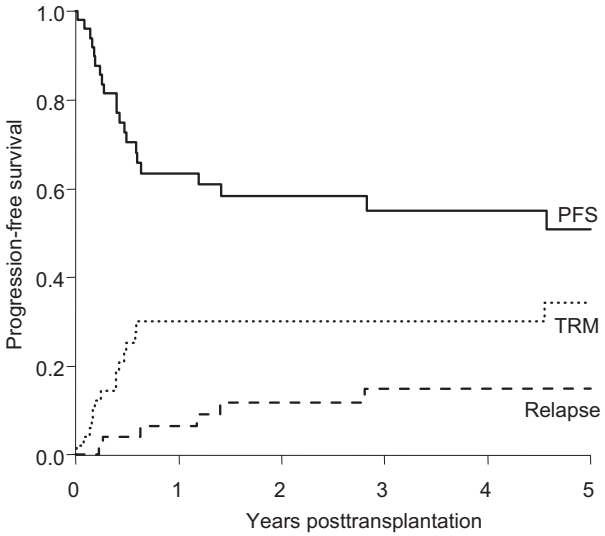

Figure 1. Progression-free survival (PFS), treatment-related mortality (TRM), and relapse incidence of 50 patients with advanced lymphoma treated with allogeneic HSCT after conditioning with BEAM/fludarabine/TBI.

Disease Response

By day 30, 1 patient (2%) had died of treatment-related complications. Of the remaining patients, 88% were in CR, 10% in PR, and 2% had a stable disease status at day 30. The patient with stable disease reached a CR without further therapy 3 months posttransplantation. As for the patients in PR at day 30, 1 died of GVHD shortly thereafter; 2 achieved CR without further therapy at 6 months and 2 years post-transplantation, respectively; 1 achieved CR after a subsequent cycle of chemotherapy; and 1 patient remains in a stable PR at 4 years of observation.

OS and PFS

With a median follow-up of 3.4 years, 30 patients (60%) were alive at last data collection. Kaplan-Meier estimated PFS at 3 years was 55% (95% confidence interval [CI], 40-70 40% to 70%), with 30% (95% CI, 19% to 47% 19-47) TRM, and a relapse incidence of 15% (95% CI, 7% to 32%, Figure 1). Three-year OS rate was 61% (95% CI, 46% to 75%). Fifteen patients (30%) died of TRM. The cause of treatment-associated death was GVHD in 10 patients, infection in 4 patients, and cerebral hemorrhage in 1 patient, as described above. At last follow-up, 5 patients (10%) had died of relapse. In 1 patient with CLL, remission was only partial but has been maintained for over 5 years.

To analyze further the impact of disease characteristics on transplantation outcome, we used a multivariable Cox model. The development of aGVHD grade II-IV strongly correlated with a poor outcome (hazard ratio [HR], 10.1, 95% CI, 2.16-47.7, $P = .003$), whereas development of cGVHD showed a protective effect, which did not reach the level of statistical significance. Notably, remission status at transplantation had no significant impact on the success of the transplantation procedure in either multivariate or univariate analysis (Figure 2A). Similarly, a history of failed autologous transplantation had no detrimental effect on OS (5-year OS rates of 57% and 47% for patients with and without previous autologous transplantation, $P = .20$).

There was a trend toward poorer survival for recipients of unrelated donor compared to sibling donor allografts (multivariable HR 2.21, $P = .12$; univariate 3 year OS 40% versus 74%, $P = .05$, Figure 2B). When patients were grouped according to histology, no significant differences in OS were noted, although the number of patients in each group was small (N = 5-23, $P = .69$, Figure 2C). In Cox modeling, patients with histologically aggressive disease showed a trend toward worse outcome (Table 2). In accordance with previous studies, development of aGVHD had a detrimental effect on survival, whereas cGVHD was found to be protective.

DISCUSSION

Relapse and progression of lymphoma and CLL after both standard and high-dose chemotherapy are common [24,25]. In such cases, prognosis is poor and there is no optimal strategy established. Allogeneic SCT is potentially curative in this situation [26]. However, opinions are split on which patients should be offered allogeneic SCT. Recommendations further diverge on which conditioning regimen to use and on what intensity it should bear. After myeloablative conditioning regimens, relapse rates of less than 20% have been documented, although at the cost of high TRM rates of up to 65% [27,28]. Reduced-intensity protocols demonstrate lower treatment-associated mortality, but relapse rates seem to be higher than after myeloablative regimens [29-31]. The cytostatic constituents of the conditioning regimen vary, frequently including fludarabine, TBI, or busulfan combined with cytarabine or melphalan [5,32,33].

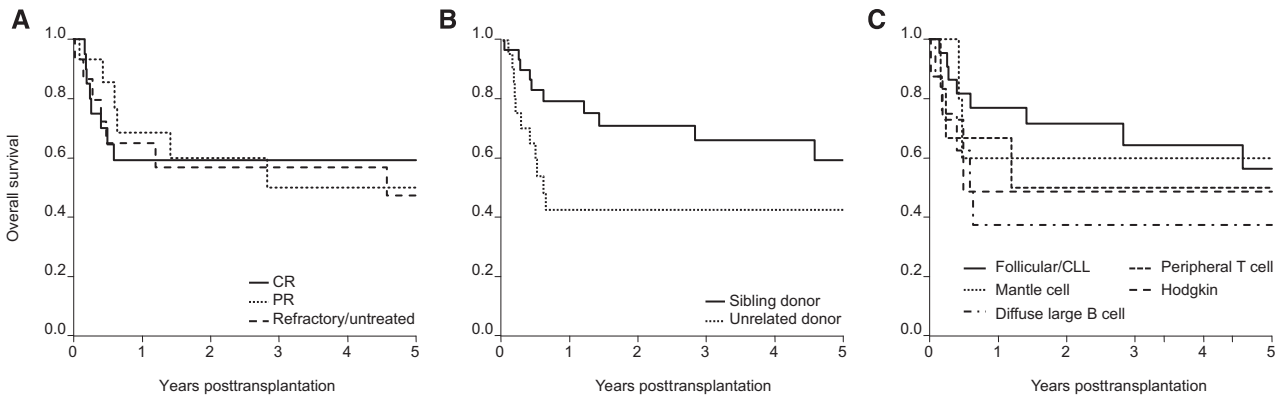

Figure 2. Overall survival in patients stratified according to disease stage at transplant (CR, complete remission; PR, partial remission; $P = .85$) (A); by the donor type ($P = .05$) (B); and by disease histology (CLL, chronic lymphocytic leukemia; $P = .69$) (C).

Table 2
Factors Affecting Overall Survival in Cox Analysis

Risk Factor	HR	95% CI	*P* value
Response status at transplant			
CR	1.00	-	-
PR	0.73	0.21-2.46	.61
Refractory/untreated relapse	0.75	0.24-2.32	.62
Donor type			
Unrelated versus related	2.21	0.81-6.03	.12
Histology			
Aggressive versus indolent	2.75	0.96-7.85	.06
aGVHD*			
Grade II-IV versus 0-I	8.97	1.92-42.1	.005
cGVHD*			
Present	0.53	0.14-1.91	.33

HR indicates hazard ratio; CI, confidence interval; CR, complete remission; PR, partial remission; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease.

* Coded as time-dependent covariables.

BEAM chemotherapy has shown low-transplantation toxicity as a conditioning regimen for the autografting and allografting of lymphoproliferative malignancies [34-38]. As mixed chimerism was reported after conditioning with BEAM and alemtuzumab [39], we supplemented etoposide dose-intensified BEAM chemotherapy with 3 days of fludarabine and a 2 Gy dose of TBI [13], based on data that the combination of fludarabine and TBI allows consistent engraftment without adding substantial toxicity [40]. This combination was historically established in a protocol in which BEAM chemotherapy without stem cell support was followed 28 days later by fludarabine/TBI and allogeneic SCT [41]. Because of high infectious morbidity associated with the prolonged aplasia in this protocol, the regimen was condensed with BEAM and fludarabine being administered in parallel and immediately followed by TBI and SCT.

In this set of 50 patients with poor-risk lymphoma or CLL, high remission rates and a low incidence of relapse were achieved. Importantly, the regimen produced long-term survival in otherwise ill-fated patients such as those experiencing relapse after a previous BEAM/autograft procedure. This fact, along with several patients in this cohort converting to CR during follow-up, demonstrates the importance of the graft-versus-tumor effect in this approach. Further support for this comes from the reduced relapse risk and improved survival in patients experiencing cGVHD, although relapse rates were overall too low for these associations to reach the level of statistical significance.

A previous multicenter trial performed allogeneic transplantation after a conditioning regimen combining BEAM with the anti-CD52 Ab alemtuzumab [39]. Although the addition of alemtuzumab effectively prevented GVHD grade >II, a substantial portion of patients experienced either primary graft failure or developed mixed chimerism, necessitating the administration of donor lymphocyte infusion. Furthermore, outcome of the high-risk subgroup of patients with a relapse after previous autologous SCT was poor in this study, suggesting that BEAM/alemtuzumab might be an optimal choice for patients with a lower risk of relapse. We found the BEAM/fludarabine/TBI regimen to be effective in patients at high risk of relapse with active disease at transplantation, regardless of disease histology or of a history of prior failed autograft. Unfortunately, definitive conclusions on predictive factors cannot be drawn because of the sample size and study design.

Although introducing allogeneic SCT into clinical courses that failed to remit under conventional treatment allowed more than one-half of the patients to attain long-term survival, 30% died of TRM. AGVHD led to death in 10 patients, followed by infection as the cause of death in 4 patients. The rate of GVHD as well as mucositis incidence and severity were significantly higher when compared to those reported after similar BEAM-based protocols [39,42]. We believe that etoposide dose-intensification, radiation-induced mucous membrane injury, plus a drug interaction between fludarabine and melphalan, may have all increased the incidence and severity of mucositis in our protocol [43-45].

To reduce the incidence of GVHD, higher MMF dosages and a delayed tapering starting on day 40 with a targeted stop on day 96, as endorsed by the Seattle trials, should permit us to diminish the GVHD occurrence in unrelated SCT [46]. Following the results published by Finke et al. [47], we are now also supplementing unrelated SCT with polyclonal anti-T cell globulin infusions in a further attempt to reduce the incidence of aGVHD. However, this measure will attenuate the graft-versus-tumor effect and may thereby raise the risk of recurrences. We believe that the comparatively low relapse rates observed in this series should allow for this sanction and for a reduction of the conditioning intensity (eg, by omission of TBI and a cutback in the etoposide dose-intensification in order to also diminish mucosal toxicity).

In conclusion, allogeneic SCT after BEAM/fludarabine/TBI provides excellent disease control in patients with poor-prognosis lymphoma or CLL. The regimen seems to overcome prognostic markers traditionally associated with poor outcome such as active disease at transplantation and history of failed autograft, making it particularly suitable for the treatment of high-risk patients. However, the high rate of TRM mainly due to aGVHD calls for further modification of the regimen.

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